REMARKS

In response to the Office Action dated July 26, 2007, Applicants submit the following remarks.

1. Amendments to the claims

Claims 1, 25-27 and 33 are currently amended; claims 2, 4-7, 16-17 and 39-56 are cancelled; and claims 18, 19, 22 and 38 are withdrawn as being directed to non-elected species/inventions. Claims 1, 3, 8-15, 20-21 and 23-37 are pending and currently under examination. Applicants reserve the right to prosecute any canceled subject matter in a continuing or divisional application.

Support for the amendment to claim 1 can be found throughout the specification such as, for example, at pages 10, 11, 13, 14, 24 and 25. As discussed further below, the amendment identifies a range of amino acid residues of a linker as disclosed in the specification. The amendments to claims 25-27 do no more than correct spelling errors. The amendment to claim 33 does no more than italicize scientific names of insect cells. Thus, Applicants assert that no new matter has been introduced by amendment. Applicants submit that the Application is in condition for allowance and respectfully request reconsideration of the rejections of the claims in light of the following arguments.

2. Examiner Interview of September 10, 2007

Applicants thank Examiner Schwadron for his time and suggestions during the telephonic interview of September 10, 2007. Applicants note that the Examiner recognized additional supporting language within the specification for any number of amino acids from 1 to 30, inclusive, that comprise a TCR constant region linker of the invention. Applicants have amended the claims, as described above, to comport with such description and support such amendments with remarks below.

3. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1, 3, 8-15, 20, 21 and 23-27 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Examiner states at page 2 of the Office Action:

> There is no support in the specification as originally filed for the recitation of "Cbeta of Calpha region is thirty amino acids or less" in claim 1.

Applicants respectfully disagree.

The specification provides support for the range of amino acids currently recited in the claims throughout the specification and figures. Specifically, the paragraph beginning at line 27 of page 24 continuing to line 3 of page 25 discloses:

> The term "segment" or "portion," when referring to a constant region in the present invention, does not include all of the constant region of the TCR, but may include about 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, or 30 contiguous amino acid residues. Any integer number of codons may be present in the linker region, including any integer number from 1 to about 30, inclusive.

The specification discloses at lines 11-12 of page 24 that "[t]he linker sequence may be a synthetic sequence to allow convenient cloning, or it may be a portion of the C_α or C_β of a TCR." The specification further discloses at lines 21-24 of page 24 that "[i]f the linker region comprises a portion of the C_α or C_β of a TCR, it may comprise some or all of the amino acids between the start of the constant region and the first cysteine residue of the immunoglobulin fold." Finally, the specification also states at lines 10-12 of page 14 that "[i]n further preferred embodiments, the linker region in either or both of the chimeric proteins may comprise a portion of a TCR constant region which is about 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, or 30 contiguous amino acid residues."

The present application discloses in, for example, pages 20, 29, the Examples and the Figures, recombinant techniques for making chimeric proteins as currently recited in the claims. One would understand that the recombinant techniques described could be used to make a chimeric protein with a TCR C_α or C_β linker region having an integer number of amino acids including any integer number from 1 to about 30, inclusive, further having the desired characteristics described in the specification as a whole.

The Examiner states, in the last paragraph on page 2 continuing to the top of page 3, of the Office Action:

> Thus, said teaching is limited to the use of constant region from the original TCR from which the Vbeta or Valpha was derived. The claims under consideration encompass use of a Cbeta or Calpha region that is thirty amino acids or less and derived from any TCR. Regarding the cited passages of the specification, page 13-14, said passages also appear to refer to the constant region that is naturally associated with a specific TCR V region.

Applicants respectfully disagree.

The specification provides support for the use of a C_α or C_β of any TCR in the specification. Specifically, lines 11-12 of page 24 state "[t]he linker sequence may be a synthetic sequence to allow convenient cloning, or it may be a portion of the C_α or C_β of a TCR." (emphasis added). Similarly, lines 10-12 of page 14 state "[i]n further preferred embodiments, the linker region in either or both of the chimeric proteins may comprise a portion of a TCR constant region which is about 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, or 30 contiguous amino acid residues." (emphasis added). Additional support for the use of a C-region from any TCR can be found, for example, at lines 17-20 of page 13 which similarly state "the linker region in either or both of the chimeric proteins may comprise a portion of a TCR constant region which is about 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, or 30 contiguous amino acid residues." (emphasis added).

Thus, there are multiple references within the specification to the use of a linker that is a portion of a C_α or C_β of a TCR which support the use of a C-region that is not associated with the TCR V_α or V_β derived from the patient.

The Examiner further states at page 3 of the Office Action:

> In addition, said passage is restricted to use of IgGgamma1 Ig heavy chain and kappa light chain and refers to the use of the entire Vbeta region.

Applicants respectfully disagree.

The specification provides support for the use of at least a portion of a V_α or V_β as recited in the current claims. For example, line 28 of page 23 continuing to line 4 of page 24 states that "[t]he terms V_α and V_β also refer to portions or segments of the V_α or V_β chains. A segment of a V_α or V_β chain may include at least about 30 amino acids of the V region. A segment of the V_α or V_β chain may also include all or substantially all of the V region." Similarly, lines 6-7 of page 10 state "[e]ach chimeric protein has at least a portion of a V_β or V_α chain of a TCR linked to at least a

portion of an immunoglobulin constant region." Still further support can be found at lines 5-7 of page 11, which state that "the V_α and/or V_β portions of the receptors specifically involved in the T cell pathology can be used to make chimeric proteins which can be expressed in a baculovirus system as described herein."

With regard to the use of IgGgamma1 Ig heavy chain, Applicants respectfully direct the Examiner's attention to lines 8 – 11 on page 11 which state "[t]he immunoglobulin constant regions used in the above compositions and chimeric proteins can be a portion of a protein selected from the group consisting of IgG_1, IgG_2, IgG_3, IgG_4, IgA, IgA_1, IgA_2, IgM, IgD, IgE heavy chains, κ and λ light chains." Additionally, lines 27-28 of page 25 further state that "[i]mmunoglobulin types include IgG_1, IgG_2, IgG_3, IgG_4, IgA, IgA_1, IgA_2, IgM, IgD, IgE heavy chains, κ and λ light chains or segments thereof," and lines 27-28 also state "[t]he terms 'IgG_1, IgG_2, IgG_3, IgG_4, IgA, IgA_1, IgA_2, IgM, IgD, IgE' refer to classes and subclasses of human immunoglobulins. The terms may refer to either the DNA sequences or amino acid sequences of the proteins."

Thus, there are multiple references to the use of less than the entire V_α or V_β chains, as well as to the use of alternate Ig heavy chains that can be used in the chimeric proteins as claimed.

Applicants submit that, when read as a whole, the specification provides sufficient guidance and direction as to how to make and use the compositions as currently claimed in order to treat T cell mediated pathologies and respectfully request reconsideration and withdrawal of the rejection.

4. Rejections under 35 U.S.C. § 103(a)

A. Weidanz et al. , Lebowitz et al.

Claims 1, 3, 8-15, and 23-36 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weidanz et al. (WO 99/18129) in view of Lebowitz et al. (*Cellular Immunology* (1999) 192: 175-184).

The Examiner states at page 4 of the Office Action that "Weidanz et al. disclose a TCR Vbeta/Calpha attached by a linker to a Valpha/Calpha wherein said construct is linked to human Ig C kappa constant regions."

Applicants respectfully disagree for the reasons discussed below.

To establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). MPEP §

2143.03. "A prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP § 2142.

Remarks regarding the Weidanz et al. reference

Weidanz et al. disclose a single chain TCR with both V regions covalently coupled in a polypeptide to a light chain constant region (see, e.g., the Summary of the Invention).

Current independent claim 1 requires that "said Vβ and said Vα are associated with a particular TCR from a T cell from said patient having said T cell mediated pathology."

In contrast to Weidanz et al., the construct as currently claimed does not include both V_α and V_β regions covalently coupled in a polypeptide to form a single chain TCR. Nor do Wiedanz et al. disclose the use of a chimeric protein comprising either the V_α or V_β region coupled via a C-region linker to an Ig heavy chain. Furthermore, Wiedanz et al. do not disclose a chimeric protein comprising a V_α or V_β region coupled via a C-region to human Ig heavy chain constant region and a V_α or V_β region coupled via a C-region to human κ or λ constant regions as currently recited in the claims of the present application.

Weidanz et al. do not disclose the use of a construct containing V_α or V_β regions associated directly with a TCR derived from the specific patient to be treated or, further, that the construct would not be used for any other patient having the same disease as is described and claimed in the present application. Rather, Weidanz et al. describe the use of *multiple* patients as a biological source for V region DNA on lines 16-30 at page 22:

> More specifically, when it is desired to obtain TCR V region DNA from a biological source, a DNA segment encoding the desired V-α and V-ß chain can be obtained from cells such as T-cell hybridomas or cytotoxic T-cells (CTLs). The T-cells (e. g., Ts, Tc or TH cells) can be obtained in vivo, or the T- cells can be cultured T-cell hybridoma (s) (e. g., D10 or B12 cell lines). See Example 1 which follows. CTLs can be uninduced or can be associated with a pathogenic immune system response in a rodent (e. g., mouse, rat, rabbit) or primate (e. g. human or chimpanzee). For example, CTLs or other T-cells can be derived from patients suffering from or suspected of having Lyme disease, Kawasaki disease, leprosy, cancer (i. e. immune responses against tumor associated antigens such as CEA), or an autoimmune disorder, particularly those associated with transplantation rejection, multiple sclerosis, insulin dependent diabetes, rheumatoid arthritis, and allergies; or an infectious disease, particularly an infectious disease involving an RNA or DNA virus.

Weidanz et al. refer to the use of multiple patients having a similar disease to obtain DNA from T-cells implicated in the disease from multiple patients; the derived construct is then administered to *any* person having the given disease.

Weidanz et al. are not concerned with personalized medicine where the patient to be treated is the sole source of the T-cell receptor gene used to generate the chimeric protein for the therapy.

The compositions described and claimed in the present application seek to target the T-cells that are the source of the disease in each individual patient by providing the receptors from T-cells (the "idiotypes") as an immunogen to the patient from which they were originally isolated, thereby achieving exquisite specificity in personalized therapy. In contrast, Weidanz et al. merely state that the TCR V region sequences may be obtained from groups of patients who have the disease to be treated, and there is no teaching that the sequences should be taken exclusively from a particular patient who is to be treated.

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc., v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). MPEP §2141.02 (VI). Weidanz et al. state at the bottom of page 2 continuing to page 3:

> Although synthesis of heterodimeric TCRs has been reported to enhance soluble expression in some cases, the methods have substantial shortcomings. For example synthesis often requires cotransfection of DNA into specialized cells which must correctly assemble the multiple protein chains. These methods often substantially reduce yields of functional heterodimeric $\alpha\beta$ TCR.
>
> Significantly, the Cκ chain has been reported to negatively impact TCR heterodimer expression. For example, it has been suggested that replacing the Cκ chain may improve TCR heterodimer valency in some cases. Further, chimeric Vβ chains comprising Ck regions have been disclosed as being particularly difficult to process, secrete, and/or fold.

Weidanz et al. teach that forms of TCRs other than the sc-TCRs disclosed within their application have "substantial shortcomings" and are difficult to "process secrete, and/or fold." One reading the Weidanz et al. disclosure would not readily choose to apply the Weidanz et al. methodologies to TCRs other than the sc-TCRS described therein. Thus, Applicants assert that Weidanz et al. teach away from the currently recited claims which are based on patient-specific personalized care.

One of ordinary skill in the art could not predict the response of a patient's immune system described by Weidanz et al. to the insect-produced TCR protein when it was administered as an

immunogen because of the different insect cell glycosylation prior to the present application. Prior to the present application, it was certainly possible that the immune response to the patient's chimeric sc-TCR protein having the insect cell glycosylation may not occur at all, possibly causing the immunization process against the T-cells involved in the targeted disease to fail.

Given the unpredictability of immunizing with a chimeric sc-TCR protein having insect cell glycosylation, one of skill in the art at the time of filing the present application would not have selected insect cell as a means of producing the required idiotypic proteins associated with the individual patient's T-cell mediated disease. It would have been entirely uncertain as to whether any potential advantages of Weidanz et al. would apply to an insect cell protein production system that is not as well characterized as, for example, Chinese Hamster Ovary (CHO) cells. Prior to the present application, the uncertainty would have been exacerbated by the wide variety of patient-specific TCR protein sequences to be synthesized in order to provide patient-specific treatment.

A recent survey of biotechnological products published in *Nature Biotechnology* reveals that the vast majority of therapeutic products are produced in *E. coli* or CHO cells: "[t]o date, virtually all recombinant proteins approved for human use are produced in either engineered *Escherichia coli* and *Saccharomyces cerevisiae*, or in animal cell lines (Chinese hamster ovary or baby hamster kidney)." Gary Walsh, Biopharmaceutical benchmarks – 2003, 21 *Nature Biotechnology* 865, 869 (2003). At the time of filing of the present application, one of ordinary skill in the art would have also been aware that the lack of experience with insect cell production systems would potentially cause a heightened review from regulatory agencies confronted with a novel (with regard to the production of therapeutics) protein synthesis system. Thus, Applicants submit that a mere statement by Weidanz et al. that insect cells could be used to produce the constructs described would not have prompted one of ordinary skill in the art to use such insect cells due to differences in glycosylation.

Applicants submit that Weidanz et al. cannot serve as a 103(a) reference as it does not disclose the chimeric proteins as currently recited in the claims of the present application. Furthermore, Applicants submit that the Weidanz et al. reference, when combined with Lebowitz et al., fails to teach every element of the currently recited claims and, therefore, cannot anticipate or render obvious the currently recited claims as discussed in more detail below.

Remarks regarding the Lebowitz et al. reference

Current independent claim 1 requires "at least a portion of a heavy chain immunoglobulin constant region" and "at least a portion of a light chain immunoglobulin constant region." The claimed compositions do not recite the variable portion of the immunoglobulin (Ig) heavy and light chains and, therefore, exclude the variable Ig portions.

The Lebowitz et al. reference discloses a chimeric protein construct comprising a TCR α chain fused to a full length IgG heavy chain (i.e., variable and constant regions) and a TCR β chain fused to a full length IgG light chain (i.e., variable and constant regions). The Lebowitz et al. TCR chains are connected to the Ig molecules via is a 6 amino acid linker between the TCR chains and the IgG chains. Thus, the structure of the Lebowitz et al. molecules differ from those as currently claimed.

The TCR used for the chimeric protein by Lebowitz et al. was a previously described clone "2C TCR" (see Materials and Methods at pages 176 and 177). MHC class I-specific 2C CTL clone (Kranz et al. (1984) PNAS USA 81: 573-577; Exhibit A) is specific for a naturally processed endogenous peptide, p2Ca, derived from α-ketoglutarate dehydrogenase bound by the murine class I molecule H-2 Ld (see second full paragraph, left column of page 179 of Lebowitz et al.).

Kranz et al. describe the administration of P815 mastocytoma cells (i.e., neoplastic mast cells) to mice in order to give them disease and constructs comprising a TCR variable region (2C TCR) derived from the P815 mastocytoma cells. Thus, the cells were artificially produced in a murine animal model. The mice of the Lebowitz et al. reference do not have mastocytoma, nor are the mouse treated with a chimeric protein which comprises a T cell idiotype from the mouse. Rather, the mice are subjected to an external agent that causes disease and are treated with a component of that external agent.

In contrast, the present application is concerned with administering two chimeric proteins which comprise the patient's own T cell receptor Vα and/or Vβ idiotype recombinantly fused to at least a portion of an Ig heavy or light chain constant region. This is not disclosed or appreciated in the Lebowitz et al. reference, which does not teach obtaining variable region sequences from the T cell mediated pathology of the patient to be treated (and which pathology is not artificially produced with a cell line). Thus, Lebowitz et al. were faced with a different problem to that solved by the present invention. Lebowitz et al. used an externally derived cell line (P815) which causes disease

in the mouse; this cell line is used to externally maintain material away from the animal suffering from the disease to allow the material to be genetically characterized. The gene isolated by Lebowitz et al., therefore, can be leisurely cloned from a plentiful supply from the 2C TCR cell line.

Lebowitz et al. do not describe using only the constant regions of the IgG heavy and light chains as opposed to the full length variable and constant regions. Finally, Lebowitz et al. make no mention of using TCR chains isolated from a specific patient who is to be treated, which construct would not be used to treat any other patient.

Furthermore, Lebowitz et al. disclose a chimeric protein having the structure discussed above, with the function of binding and/or identifying its cognate MHC. The linkage of the TCR chains to the full length IgG variable and constant chains increases the valency and avidity of the TCR binding to bind its cognate ligand (i.e., a specific MHC) to further improve its use as a probe or diagnostic binding agent to study cell-cell interactions (*see* the Abstract at p. 175; Discussion, first paragraph at p. 183; Discussion, last paragraph at p. 184). There is no teaching of using the TCR construct for immunization for personalized patient care in a manner as described in the present specification and as currently claimed.

This is in marked contrast to the constructs of the present invention which are designed to rapidly produce two chimeric proteins with at least portions of Vβ or Vα genes cloned from a biopsy from the patient to be treated and portions of an immunoglobulin (Ig) light or heavy constant region. The present invention allows such chimeric proteins to be created using an insect cell and used to alter a T cell mediated pathology.

In conclusion, the teachings of Weidanz et al. and Lebowitz et al. fail to teach every element of the currently recited claims, either alone or in combination. Given that Weidanz et al. further teach away from making and using a construct as currently recited in the present claims and the unpredictability in the art at the time of filing with respect to producing therapeutic constructs in insect cells, Applicants assert that the combination of references cannot render the claimed constructs *prima facie* obvious.

In view of the amendments to the claims and the remarks presented herein, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Weidanz et al. , Lebowitz et al. and Brostoff et al.

Claim 37 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weidanz et al. (WO 99/18129) in view of Lebowitz et al. (*Cellular Immunology* (1999) 192: 175-184), and in further view of Brostoff et al. (WO 94/25063).

Weidanz et al. and Lebowitz et al. have been discussed above.

The Examiner states at the bottom of page 5 of the Office Action that "Brostoff et al. teach treatment of T cell lymphoma by administration of TCR derived from a T cell lymphoma."

Applicants respectfully disagree.

The structure of the constructs administered in the methods as currently recited are discussed above. Claim 1 also requires that the "V_β and said V_α region are associated with a particular TCR from a T cell from said patient having said T cell mediated pathology. . . and said administering of said composition alters said T cell mediated pathology in said patient."

Brostoff et al. do not describe TCR chains, or segments thereof, joined to an Ig constant region by a linker. Furthermore, the TCR chains used by Brostoff et al. are derived from multiple sources, and representative TCR chains of the disease in these subject groups are then selected for use as a general immunogen:

> As they relate to autoimmune disease, the vaccines of the present invention comprise TCRs of T cells that mediate autoimmune diseases. The vaccines can be whole TCRs substantially purified from T cell clones, individual T cell receptor chains (for example, alpha, beta, etc.) or portions of such chains, either alone or in combination. The vaccine can be homogenous, for example, a single peptide, or can be composed of more than one type of peptide, each of which corresponds to a different portion of the TCR. Further, these peptides can be from distinct TCRs wherein both TCRs contribute to the T cell mediated pathology.
>
> The Vβ6 TCR subunits were sequenced from 8 patients. From these 8 patients three-quarters (6 of 8) were identified as members of the VB5.2/3 and Vβ6.5 subfamily shown in Figure 2. These two subfamilies of the VB6 gene family show considerable homology in the CDR2 region between residues 39 and 58. It appears that these two particular members of the Vβ6 family are particularly associated with multiple sclerosis.
>
> In a further specific embodiment, T cell receptors, whole T cells or fragments of the TCR which contain the Vβ chains designated Vβ6.2/3, Vβ6.5, Vβ2, Vβ5.1, Vβ13, Vβ7 can be used to immunize an individual having or at risk of having multiple sclerosis to treat or prevent the disease. The immune response generated in the individual can neutralize or kill T cells having the particular Vβ subunit and, thus, prevent or treat the deleterious effects of the

> Vβ-bearing T cells. Moreover, to the extent that these Vβ subunits are common to T cell receptors on pathogenic T cells mediating autoimmune diseases in general, such vaccines can also be effective in ameliorating such other autoimmune diseases.

See line 27 of page 12 continuing to line 25 of page 13.

When discussing the selection of TCR chains for immunization at lines 12-16 of page 9, Brostoff et al. describe the rationale for utilizing a TCR chain common across a patient or disease pool, stating:

> These findings confirm the notion of common TCR structure among T cells with similar antigen specificities and indicate that the TCR is an effective target for immunotherapeutic strategies aimed at eliminating the pathogenesis of EAE.

Thus, Brostoff et al. are concerned with representative TCR chains rather than the personalized therapy with TCRs derived from a particular patient to be treated as described and claimed in the present application.

Additionally, as noted above, a reference must be considered as whole, including any portions that may teach or suggest away from the claimed invention. *W.L. Gore & Associates, Inc., v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). MPEP §2141.02 (VI). Applicants assert that Brostoff et al. explicitly teach away from the personalized medicine concept of the as claimed in the present application. When describing the problems with alternative techniques for T-cell receptor immunization, such as immunization with whole T-cells, Brostoff et al. teach at lines 5-9 of page 11 that "individualized therapies" are to be avoided:

> . . . it requires <u>in vitro</u> cultivation with attenuated disease-inducing T cells to develop clones of such regulatory T cells, a costly and labor intensive process. Further, in an outbred population such as humans, MHC non-identity among individuals makes this a highly individualized therapeutic strategy. Regulatory clones need to be derived for each individual patient and then re-administered only to that patient to avoid potential graft versus host reactions.

Brostoff et al. further teach at lines 5-12 of page 12:

> Thus, vaccination with attenuated disease-inducing T cells suffers from a lack of specificity for the protective antigen on the surface of that T cell, as well as, variable induction of immunity to that antigen. As a candidate for the treatment of human diseases, vaccination with attenuated T cells is plagued

> by the same labor intensiveness and need for individualized therapies as noted above for infusion of CD8+ cells

Following identification of problems associated with individualized therapy, Brostoff et al. then disclose how their method avoids the problems typically associated with whole-cell immunization and individualized therapy – namely through the identification of representative TCRs associated with specific diseases as the source for the vaccine and the use a TCR or segment thereof for vaccination, stating "[t]he present invention provides an effective method of immunotherapy for T cell mediated pathologies, including autoimmune diseases such as multiple sclerosis, which avoids many of the problems associated with the previously suggested methods of treatment." (See lines 13-17 at p. 12). Clearly, Brostoff et al. are not concerned with individualized therapy – rather, they teach away from it.

As discussed above, Applicants assert that the combination of Weidanz et al. and Lebowitz et al. do not anticipate or render obvious the claimed invention alone or in combination and, further, that the addition of Brostoff et al. cannot remedy the deficiencies of the cited references from the aforementioned combination. Applicants respectfully request reconsideration and withdrawal of the rejection.

C. Weidanz et al. , Lebowitz et al. and Bonnem et al.

Claims 20 and 21 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weidanz et al. (WO 99/18129) in view of Lebowitz et al. (*Cellular Immunology* (1999) 192: 175-184), and in further view of Bonnem et al. (WO 94/01133).

Weidanz et al. and Lebowitz et al. have been discussed above.

The Examiner states at item 12 of page 6 of the Office Action that "Bonnem et al. disclose that GM-CSF can be administered to increase the immune response to administered antigen (see claim 1 and abstract)."

Bonnem et al. do not describe the chimeric proteins as presently claimed, nor any chimeric proteins. Because the aforementioned combination of Weidanz et al. in view of Lebowitz et al. does not anticipate or render obvious the claimed constructs as previously discussed, the addition of Bonnem et al. cannot remedy the deficiencies of the aforementioned combination by merely disclosing the use of GM-CSF as an adjuvant for immunization.

Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the remarks and amendments submitted herein, Applicants believe that the Application is in condition for allowance.

The three-month deadline for filing a response was October 26, 2007. Applicants hereby petition for a three-month extension of time with the relevant fees; therefore, Applicants believe that this response is being timely filed and that the fees submitted herewith are sufficient. However, in the event that Applicants are incorrect in their assumption, please charge any necessary fee to Deposit Account No. 23-2415, referencing Docket No. 30795-702.201.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (858) 350-2300.

Respectfully submitted,

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